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The Use of Planar Electromagnetic Fields in Effective Vaccine Design

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<http://dx.doi.org/10.5772/intechopen.69546>

Abstract

Vaccines have not yet been able to address the combination of three major obstacles: molecular coupling failure between peptide and human leukocyte antigen protein (HLA-II) molecule, failure to activate T-cells, and the molecular polymorphism displayed by all pathogens. Planar electromagnetic fields found in protein systems may play a role in all three problems. These amino acid planes are universal, selective in nature, and able to generate long distance attraction toward their corresponding ligand. We propose three molecular mechanisms through which to engineer molecular pattern interaction toward the intelligent design of more effective vaccines.

Keywords: vaccine design, PECC, HLA-II binding affinity, T-cell activation, molecular polymorphism

1. Introduction

Many different technologies have been developed to design different types of vaccines—biological, synthetic, genetically engineered, naked DNA and vector—and in spite of these efforts, major problems remain to be solved, preventing effective vaccines being obtained for pathogens such as HIV and malaria.

Three obstacles for current vaccines relate to the difficulty in coupling class II human leukocyte antigen proteins (HLA-II), in activating T-helper cells, and the molecular polymorphism of the pathogens.

Our search for solutions to these obstacles led to a series of significant findings, fundamental to biochemistry, and relating to: the discovery of the mechanism of molecular coupling

between peptides and HLA-II molecules; identification of the mechanism for the activation of T-cell receptor molecules; a solution to molecular polymorphism in pathogens.

2. Molecular coupling between peptides and HLA-II molecules

In the activation of immune responses, HLA-II molecules are responsible for presenting peptide antigens to T-helper cells [1, 2] to activate the cascade that accompanies this response. The coupling of HLA-II molecules with peptide antigens is therefore critical for vaccine design [3, 4] because it is necessary to induce immune memory.

All the subtypes of HLA-II molecules (DR, DP and DQ) are highly polymorphic [1, 5]. The high polymorphism of these molecules represents one of the greatest difficulties in vaccine development [2–4], as HLA-II/peptide coupling is restricted by this polymorphism.

2.1. Planar electromagnetic fields in HLA-II molecules may explain coupling with foreign peptides

Following a review of HLA-II molecules from the National Center for Biotechnology Information (NCBI) database, the constant positions of fully conserved residues in HLA-II α and β chains were identified. The positions are recorded in **Table 1**.

These positions were then located within a three-dimensional protein crystallography structure provided by the protein data bank (PDB) and examined using bioinformatic tools, whereupon geometric patterns emerged.

Fully conserved residues	Residues in the HLA-II molecules, in the α and β chains						Aromatic residue in the plane (3O6F)
	DP (3LQZ) ^a		DQ (1UVQ)		DR (1DLH)		
	α	β	α	β	α	β	
Cys (C)	107	15, 115, 171	110	15, 117, 173	107	117, 173	Phe - 151
Gly (G)	100, 131	149, 166	103, 134	151, 168	131	151, 168	Tyr - 150
Leu (L)	105, 151	113, 159	108, 154	115, 161	105, 151	115, 161	Phe - 184
Asn (N)	103	31, 60, 132, 148	106	33, 62, 134, 150	103	134, 150	Phe - 151
Pro (P)	102, 114, 115, 155	95, 122, 163	105, 117, 118, 158	97, 124, 165	102, 114, 115, 155	97, 124, 165	Phe - 137
Thr (T)	-	152, 170	-	154, 172	-	154, 172	Phe - 184
Val (V)	91	97, 117, 173	94	99, 119, 175	91, 128	99, 119, 175	Phe - 151
Trp (W)	121	129, 151, 186	124	131, 153, 188	121	131, 153, 188	Trp - 182
Tyr (Y)	150	121, 169	153	123, 171	150	123, 171	Tyr - 152

Note: ^aPDB ID are shown in parenthesis.

Table 1. Fully conserved residues of HLA-II in sequences and structures.

These molecular patterns were found in all three types of HLA-II (DR, DP and DQ). They comprise fully conserved amino acid residues arranged in a planar configuration. **Figure 1** illustrates the spatial arrangements for the amino acid residues Gly (**Figure 1a and b**) and Trp (**Figure 1c and d**).

The patterns were found to feature the conditions required to generate planar electromagnetic fields. These fields are known as planar electromagnetic fields of Cortés-Coral (PECC). PECC fields are produced by groups of invariant and fully conserved amino acids from a single chemical species (this conservation is simultaneous both in sequence and in space). There will thus, for example, be glycine planes (PECC-Gly), proline planes (PECC-Pro), leucine planes (PECC-Leu), etc. Importantly, each PECC field is generated in a single direction.

The question may arise as to how the electromagnetic field is generated. Essential to the explanation is the fact that each plane was found to possess an aromatic amino acid (e.g., Phe, Tyr, Trp) always located in a well-defined position within that plane. An aromatic amino acid has electric charges in motion (electrons). These electrons generate the electromagnetic signals that are able to act over long molecular distances, i.e., at long range. The HLA-II/peptide coupling mechanism has not been able to be explained satisfactorily by the already known intermolecular forces (Van der Waals, hydrogen bonding and ionic forces) because they act only at short range; in the case of ionic forces [6], for example, the range of

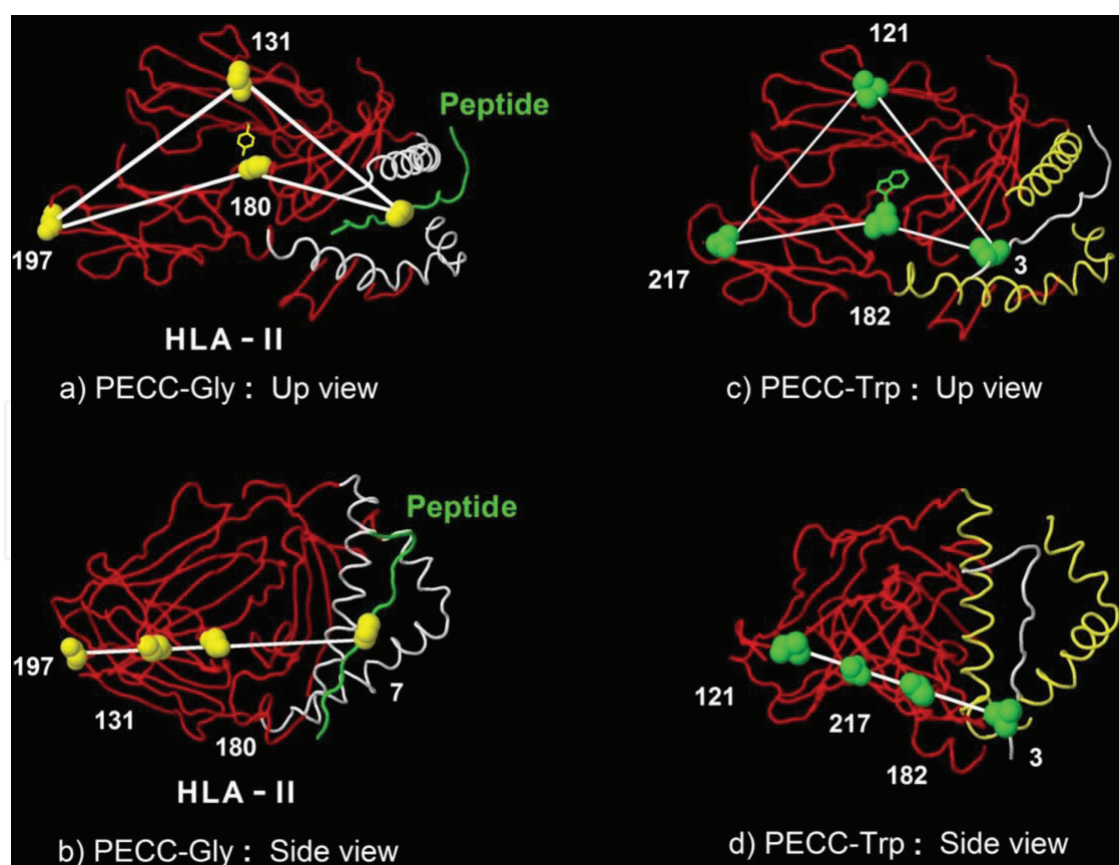


Figure 1. Spatial positions of fully conserved glycine and tryptophan residues in HLA-II DR (Images taken from Jmol 12.0, reproduced with permission of IVSI).

action is only about 2 nm [7]. It follows, therefore, that no classical concept is able to explain the long-range molecular interactions that occur between protein molecules. Further, in three-dimensional analysis of proteins and their ligands, it can be seen that the couplings do not have a well-defined or selective spatial and electrostatic complementarity, as proposed by the “key-lock” model [8, 9]. There is evidence, meanwhile, that biological processes can be induced or modulated by electromagnetic fields of characteristic frequencies, as with light in photosynthetic systems [10] or with the increase in the catalytic activity of some enzymes on being irradiated with electromagnetic fields [11, 12]. Research carried out by the School of Electrical and Computer Engineering of the RMIT University in Melbourne (Australia) shows that proteins emit and absorb electromagnetic radiation of very precise frequencies, different for each protein [8].

PECC fields, as we have seen by their planar nature, act in a single and specific direction. They are also able to act over long distances. They are therefore capable of explaining the following phenomena intrinsic to receptor-ligand coupling:

- the *directional nature* of the attraction/coupling;
- the *selectivity* required to target the correct ligand;
- the extremely *short time* period to encounter the ligand;
- and the *long distance* across which the attraction must take place.

In this context, given the three-dimensional arrangement of each PECC based on the positions of its component residues in the protein structure, each PECC field of HLA-II was projected in the direction of its plane toward the HLA-II groove pockets. Specific positions on the groove were thus associated with the PECC projections.

When a foreign peptide is in the coupled position, each of the positions identified is found to contain a residue of exactly the same species as the PECC projected there; where a PECC-Gly is projected onto the groove, a glycine residue is encountered in the coupled foreign peptide. Similarly, for a PECC-Leu projection, a leucine residue is found at that position. The PECC projections were thus able to predict residues and their positions in the groove.

The universal Class II-associated invariant chain peptide (CLIP), known for its binding affinity, was further found to have five PECC projection matches. When CLIP was modified so that it contained an additional PECC projection, its binding affinity was enhanced, suggesting that PECC fields favor the attraction of their respective residue in a peptide [13, 14].

Using PECC projections toward the groove of HLA-II molecules, a universal coupling sequence was found to be present in all HLA-II types. This is presented in **Table 2**. Note that more than one PECC may be projected toward some positions, as shown for position 1, where PECC-Trp, PECC-Tyr and PECC-Val are present.

Considering this finding further, a pattern of universal coupling was identified in all types and subtypes of histocompatibility molecule, thus permitting the design of peptide-vaccines with a capacity to couple with any polymorphic form presented by HLA-II molecules [13].

PECC position in groove of HLA-II											
-1	1	2	3	4	5	6	7	8	9	10	11
L	W	P	P	W	W	P	L	L	N	P	P
V	Y	C			T		G	P		N	
	V				G		P				

Table 2. PECC fields projected toward different positions of the HLA-II anchoring groove.

The application of this new finding made it possible to design peptides with better peptide/HLA-II coupling values than those generated by the universal coupling peptide CLIP [13, 14].

Selection and attraction between HLA-II molecules and antigen peptides in this way would therefore be nonrandom, resulting in an effective and rapid coupling mechanism, as is clearly required in the immune response. Thus, PECC fields project outwardly from the HLA-II molecule in order to select, attract, and couple specific peptide sequences (**Figure 2**).

Application of the principles of this selective and attractive force could permit the design in future of vaccine-peptides with a universal high binding affinity to HLA-II molecules. The findings would further allow new avenues to be explored involving other protein systems, including HLA-I and T-cell receptors (TCRs), necessary for understanding mechanisms of immune activation, as well as opening up possibilities for the wider study of protein receptor-ligand systems.

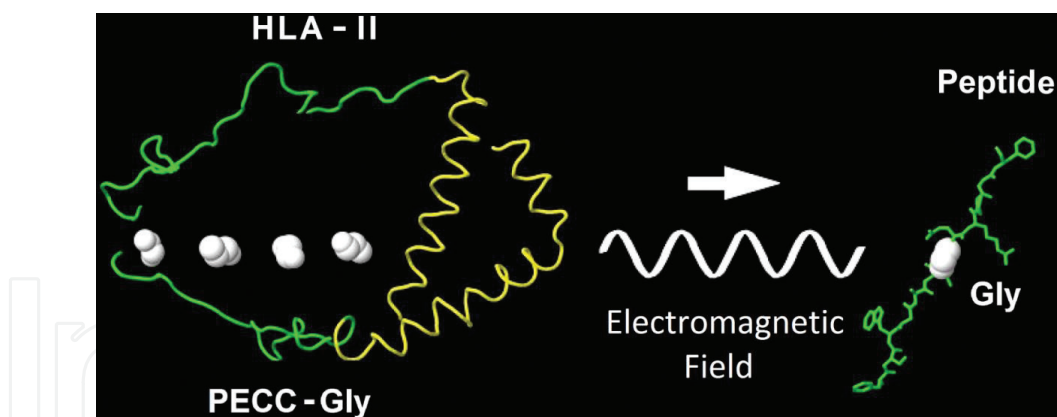


Figure 2. PECC-Gly selective, attractive force, exerted toward Gly residue in peptide (Images taken from Jmol 12.0, reproduced with permission of IVSI).

3. Activation of T-helper cells

T-cell receptors (TCRs) are molecules found on the surface of T-helper cells that are responsible for recognizing antigens bound to HLA-II molecules. This coupling is very important for immune memory, whenever activation of the TCRs occurs. TCR activation is provoked

on recognition of certain foreign antigens (T-epitopes) and is crucial to the functioning of vaccines [15, 16]. Thus, all vaccines require T-epitopes in their protein composition, acting as TCR activators. However, the mechanisms known to induce activation are not clearly understood [17]. Greater comprehension in this regard could enable the design of vaccine-peptides capable of inducing immunological memory in B and T cell lines.

A number of authors refer to the TCR as a “mechanosensor” that converts mechanical energy into biochemical signals on coupling with the antigen, whereupon transduction of the signal is induced [18, 19]. However, this mechanistic explanation is not sufficient to understand the internalization of the message induced by the ligand, since a mechanism of this type requires too much energy to induce a signal that travels all the way from the point of coupling with the ligand to the intracellular domain. This is because a mechanical signal induces multiple aimless movements, raising the entropy of the system, and dispersing the energy [20]. Moreover, such an activation mechanism would not be sufficiently specific and would lack the selectivity necessary to differentiate between the body’s own antigens and foreign ones.

Researchers at the IVSI institute put forward an explanation for understanding the molecular mechanisms of activation and transduction in the TCRs, based on the concept of PECC. The fully conserved residues found in the TCR molecules are shown in **Table 3**. These residues form a PECC system responsible for transmitting the signal of the antigen from its point of contact to the interior of the cell. This type of field was termed PECC-ionic, or PECC-i [21]. Only the alpha (α) chain of the TCR showed fully conserved residues that form part of the PECC-i. No such residues were evident in the beta (β) chain.

From physical analysis of a PECC-i, it may be inferred that all of its residues are mutually interlinked by a single electromagnetic field. This field would ensure that the residues behave in a synchronized manner. As a result, the action applied at one point (amino acid) of the PECC-i is replicated at all the other points, enabling signals to be sent from the point of contact with the ligand to the intracellular domain of the receptor [21], as shown in **Figure 3**. In **Figure 3a–c**, all the highly conserved residues of the free TCRs are seen to be in a dissociated state, while in **Figure 3d**, in which the molecule is coupled with the peptide, these same residues are paired. This shows that the coupling of opposite charges between the TCR and the peptide induces the additional formation of new pairings inside the planar system. The mechanism proposed by the authors to explain the molecular transduction of signals was named “molecular transduction by PECC-ionic” (TM-PECC-i, from the Spanish acronym) [21].

PDB	1FYT	4GKZ	3QEU	3QH3
Residues of human TCRs ^a	D135	D133	D128	D129
	K136	K134	K129	K130
	K184	K182	K177	K178
	D 186	D184	D179	D180

Note:^a Residues in the α -chain of the TCR molecule.

Table 3. Fully conserved residues in human TCR molecules that form PECC planes. Such residues occupy equivalent spatial positions in all TCRs.

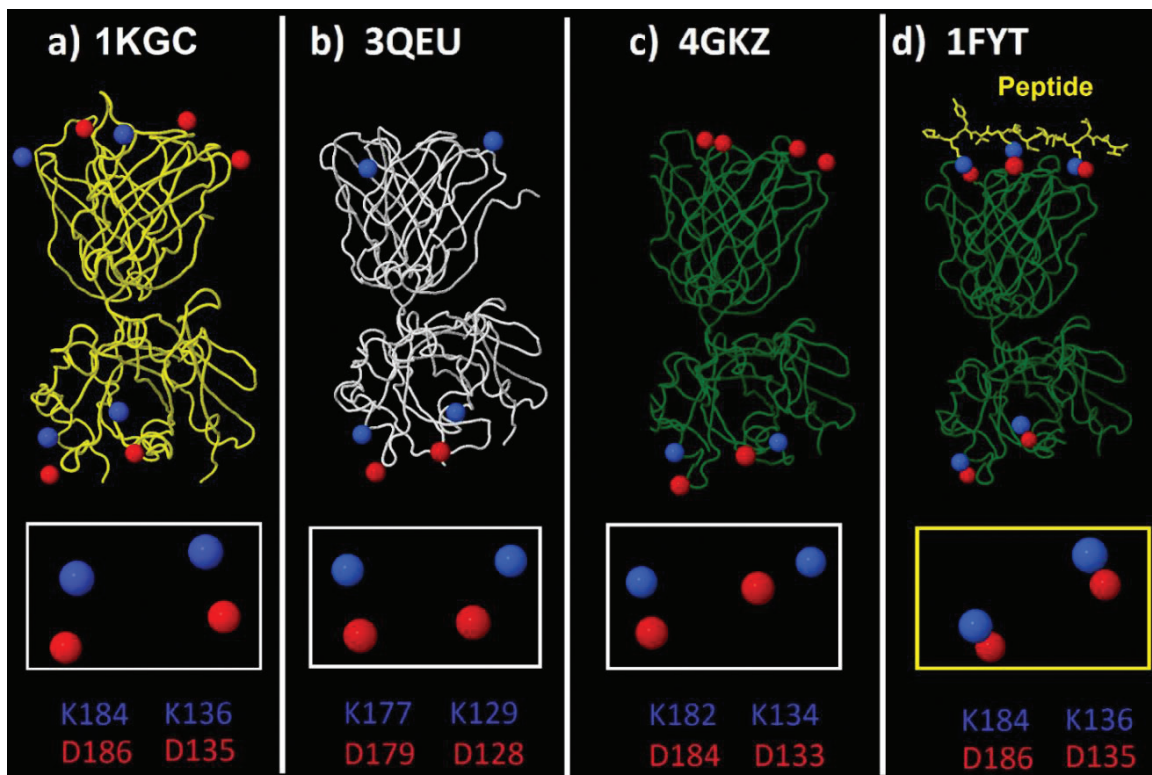


Figure 3. TCR molecules in free states (a–c) and coupled (d), showing positive and negative electrical residues as stylized spheres. The highly conserved residues are highlighted in the boxes below each figure. (Image records taken from Jmol, reproduced with permission of IVSI) [21].

4. Molecular polymorphism of pathogens

Molecular polymorphism is a mechanism that pathogenic agents employ to evade host immune responses. None of the current vaccines has managed to overcome this problem, which is why vaccination booster doses require to be applied anew each year, as in the case of influenza. The HIV virus and the malarial parasite are highly polymorphic pathogens that change their molecular sequences every time they replicate.

The IVSI Institute was the first research group in the world to find a solution to the molecular polymorphism of pathogens. The authors found that the molecular polymorphism of a pathogen is not random but rather ruled by an underlying order that allows the protein to retain its functionality while evading repeated attack by the immune system. By re-examining the molecular cell-pathogen coupling receptors in the new light of PECC fields, a solution to molecular polymorphism in pathogens was found.

The method developed by our researchers to solve the problem of the polymorphism of the virus is analogous to what happens with the bedroom door-key system in a 200-room hotel: each guest will have a key to open his/her own room, so that 200 keys will be needed to open all of the rooms. The concierge, however, is not required to carry around 200 keys. He will have a single key, or master key, to be able to open every door. Likewise, our methodology enabled us to identify the the master key used by the virus in order to couple *always with the same receptor*, despite its high

molecular polymorphism, using solid state physics tools. Using these tools together with the PECC system raises the possibility of designing effective vaccines against the polymorphic pathogen.

5. Conclusions

A novel methodology is proposed by the authors for the design of effective vaccines, based on planar molecular patterns found in proteins. These patterns were discovered in fully conserved residues of HLA-II and TCR molecules. According to the authors, these patterns generate planar electromagnetic fields, given the name PECC fields. These direct the coupling of peptides with HLA-II molecules and the activation of the TCRs in T-cells. The function of these PECC fields is to select and attract antigen-peptides for subsequent coupling with HLA-II molecules. A further type of PECC, known as PECC-ionic, is responsible for interiorizing the signal of TCR-antigen coupling to activate the T-helper cells. Moreover, the PECC concept enabled the authors to solve the problem of molecular polymorphism of pathogens, finding an underlying order in the apparent random chaos of polymorphism.

Acknowledgements

The authors express their gratitude to the Synthetic Vaccines, Antisera and New Drugs Research Institute (IVSI) Colombia for providing the infrastructure and funding for developing the model. We are also grateful to the University of Cauca for continuing support.

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References

- [1] Reinherz EL, Tan K, Tang L, Kern P, Liu J-h, Xiong Y, et al. The crystal structure of a T cell receptor in complex with peptide and MHC class II. *Science*. 1999;**286**:1913-1921
- [2] Mushtaq K, Chodisetti SB, Rai PK, Maurya SK, Amir M, Sheikh JA, et al. Decision-making critical amino acids: Role in designing peptide vaccines for eliciting Th1 and Th2 immune response. *Amino acids*. 2014;**46**:1265-1274

- [3] Desai DV, Kulkarni-Kale U. T-cell Epitope Prediction Methods: An Overview. *Immunoinformatics*. Springer; 2014. pp. 333-364
- [4] Ribeiro SP, Rosa DS, Fonseca SG, Mairena EC, Postól E, Oliveira SC, et al. A vaccine encoding conserved promiscuous HIV CD4 epitopes induces broad T cell responses in mice transgenic to multiple common HLA class II molecules. *PLoS One*. 2010;5: e11072
- [5] Wang M, Claesson MH. Classification of Human Leukocyte Antigen (HLA) Supertypes. *Immunoinformatics*. Springer; 2014. pp. 309-317
- [6] Kumar S, Nussinov R. Close-range electrostatic interactions in proteins. *ChemBioChem*. 2002;3:604-617
- [7] Beretta S, Chirico G, Baldini G. Short-range interactions of globular proteins at high ionic strengths. *Macromolecules*. 2000;33:8663-8670
- [8] Ćosić I, Pirogova E, Vojisavljević V, Fang Q. Electromagnetic properties of biomolecules. *FME Transactions*. 2006;34:71-80
- [9] Pirogova E, Cosic I, Vojisavljevic V. *Biological Effects of Electromagnetic Radiation*. INTECH Open Access Publisher; 2009
- [10] Brédas J-L, Sargent EH, Scholes GD. Photovoltaic concepts inspired by coherence effects in photosynthetic systems. *Nature Materials*. 2017;16:35-44
- [11] Vojisavljevic V, Pirogova E, Cosic I, editors. *Influence of electromagnetic radiation on enzyme kinetics*. Engineering in Medicine and Biology Society, 2007 EMBS 2007 29th Annual International Conference of the IEEE. IEEE; 2007
- [12] Vojisavljevic V, Pirogova E, Cosic I, editors. *Review of studies on modulating enzyme activity by low intensity electromagnetic radiation*. Engineering in Medicine and Biology Society (EMBC), 2010 Annual International Conference of the IEEE. IEEE; 2010
- [13] Cortes A, Coral J. Campos electromagneticos planares permiten explicar el acople entre peptidos y moleculas de HLA-II. *Acta bioquímica clínica latinoamericana*. 2015;49:221-228
- [14] Cortés A, Coral J, Benítez Benítez R. Hallazgo de patrones para péptidos-vacuna con capacidad de acople universal en moléculas de HLA-II. *Acta bioquímica clínica latinoamericana*. 2013;47:541-549
- [15] Sami M, Rizkallah PJ, Dunn S, Molloy P, Moysey R, Vuidepot A, et al. Crystal structures of high affinity human T-cell receptors bound to peptide major histocompatibility complex reveal native diagonal binding geometry. *Protein Engineering Design and Selection*. 2007;20:397-403
- [16] Wang J-H, Reinherz EL. Revisiting the putative TCR C α dimerization model through structural analysis. *Frontiers in Immunology*. 2013;4:16
- [17] Adams JJ, Narayanan S, Liu B, Birnbaum ME, Kruse AC, Bowerman NA, et al. T cell receptor signaling is limited by docking geometry to peptide-major histocompatibility complex. *Immunity*. 2011;35:681-693

- [18] Kim ST, Shin Y, Brazin K, Mallis RJ, Sun J, Wagner G, et al. TCR mechanobiology: Torques and tunable structures linked to early T cell signaling. *Frontiers in Immunology*. 2012;**3**:76
- [19] Kim ST, Takeuchi K, Sun Z-YJ, Touma M, Castro CE, Fahmy A, et al. The $\alpha\beta$ T cell receptor is an anisotropic mechanosensor. *Journal of Biological Chemistry*. 2009;**284**:31028-31037
- [20] Bischof M, Del Giudice E. Communication and the emergence of collective behavior in living organisms: A quantum approach. *Molecular Biology International*. 2013;**2013**
- [21] Cortés A, Coral J, Benítez Benítez R, McLachlan C. Campos electromagnéticos planares permiten explicar transducción en receptores de células T. *Acta bioquímica clínica latinoamericana*. 2016;**50**:657-654